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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/362,286	07/27/1999	ANUPAMA K. NADKARNI	50370-61113	6674

21874 7590 09/19/2005

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EXAMINER	
MURPHY, JOSEPH F	

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 09/19/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/362,286	NADKARNI ET AL.	
	Examiner	Art Unit	
	Joseph F. Murphy	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 July 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11,14,43-63,67 and 68* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *14, 44-59, 67* is/are allowed.

6)☒ Claim(s) *1-11,43,61-63 and 68* is/are rejected.

7)☒ Claim(s) *7, 9* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Sequence Comparison A*.

DETAILED ACTION

Formal Matters

Claims 1-11, 14, 43-63, 67-68 are pending and under consideration. Prosecution in this case had been closed in accordance with the practice under Ex Parte Quayle, and Applicant corrected the formal requirements in the reply filed 7/12/2005. However, upon further consideration new rejections are set forth below, and the Finality of the previous Office Action is withdrawn. The Examiner regrets the inconvenience.

Claim Rejections - 35 USC § 112 first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-11, 43, 61-63, 68 are rejected, under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, for reasons of record set forth in Paper No. 19, 6/12/2002. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

The claims encompass mutant mammalian GPCRs that differ from a wild-type GPCR by comprising a 4 amino acid stretch closer to the C-terminal end than the N-terminal end. The claims as written are drawn to mutants of the chemokine alpha family of GPCRs.

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice,

reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between structure and function structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. In the instant case, the specification fails to provide sufficient descriptive information, such as definitive structural or functional features of the claimed genus of mutant polypeptides. The difficulty of correlating structure to function in the protein art is shown in Bowie et al (Science, 1990, 247:1306-1310) which teaches that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instructions of the genome and further teaches that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. (col 1, p. 1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (col 2, p. 1306). Additionally, Yan et al. teaches that in certain cases, a change of only two-amino acid residues in a protein results in switching the binding of the protein from one receptor to another (Yan et al., Two-amino acid molecular switch in an epithelial morphogen that regulates binding to two distinct receptors. *Science* 290: 523-527, 2000). It is also known in the art that a single amino acid change in a

protein's sequence can drastically affect the structure of the protein and the architecture of an entire cell. Voet et al. (1990) teaches that a single Glu to Val substitution in the beta subunit of hemoglobin causes the hemoglobin molecules to associate with one another in such a manner that, in homozygous individuals, erythrocytes are altered from their normal discoid shape and assume the sickle shape characteristic of sickle-cell anemia, causing hemolytic anemia and blood flow blockages (pages 126-128, section 6-3A and page 230, column 2, first paragraph). Additionally, the Gether reference is cited to further show the unpredictability of structure to function determinations in the GPCR superfamily. Gether teaches that GPCRs do not share any overall sequence homology. The only structural feature common to all GPCRs is the presence of seven transmembrane-spanning α-helical segments connected by alternating intracellular and extracellular loops, with the amino terminus located on the extracellular side and the carboxy terminus on the intracellular side (page 91, column 1, second paragraph). The three major subfamilies of GPCR's include the receptors related to the "light receptor" rhodopsin and the β 2 -adrenergic receptor (family A), the receptors related to the glucagon receptor (family B), and the receptors related to the metabotropic neurotransmitter receptors (family C) (page 91, column 1, second paragraph). The overall homology among all type A receptors is low and restricted to a number of highly conserved key residues The high degree of conservation among these key residues suggests that they have an essential role for either the structural or functional integrity of the receptors (page 91, column 1, third paragraph). Family B receptors include approximately 20 different receptors for a variety of peptide hormones and neuropeptides, such as vasoactive intestinal peptide (VIP), calcitonin, PTH, and glucagon (page 92, Fig. 1). Except for the disulfide bridge connecting the second (ECL 2) and third extracellular loops (ECL 3), family B

receptors do not contain any of the structural features characterizing family A receptors (page 91, column 2, second paragraph). Family C receptors have, like family A and B receptors, two putative disulfide-forming cysteines in ECL 2 and ECL 3, respectively, but otherwise they do not share any conserved residues with family A and B receptors (page 92, Fig. 1 and page 91, column 2, third paragraph). The Gether reference thus teaches that the GPCR superfamily is large and diverse, and that residues necessary for function are not shared between families, and even within families, residues critical for function are not known. These references demonstrate that even a single amino acid substitution will often dramatically affect the biological activity and characteristics of a protein.

As set forth *supra*, it is known in the protein art that correlating structure to function is difficult based upon the evidence presented in the Bowie et al. reference showing that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex, the Yan et al. and Voet et al. references which demonstrates that the change of only one or two amino acids can radically alter protein function and the Gether reference which teaches that the GPCR superfamily is large and diverse, and that residues necessary for function are not shared between families, and even within families, residues critical for function are not known. Applicant has disclosed a mutant IL8 receptor and a mutant galanin receptor, but has not described a polypeptide comprising a functional mutation of the chemokine alpha GPCRs. The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical

and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between structure and function structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. In the instant case, the specification fails to provide sufficient descriptive information, such as definitive structural or functional features of the genus of polypeptides used in the claimed method. There is no description of the conserved regions which are critical to the structure and function of the genus claimed. There is no description of the sites at which variability may be tolerated and there is no information regarding the relation of structure to function. Structural features that could distinguish the compounds in the genus from other seven transmembrane region compounds are missing from the disclosure. Furthermore, the prior art does not provide compensatory structural or correlative teachings sufficient to enable one of skill to isolate and identify the polypeptides encompassed: there is no guidance in the art as to what the defining characteristics of the polypeptides might be. Thus, applicant was not in possession of the claimed genus.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 5, 8, 11, 43 are rejected under 35 U.S.C. 102(b) as being anticipated by Kluxen et al. (1992).

The claims are drawn to a mammalian GPCR that comprises a four amino acid motif closer to the C-terminal end, wherein there is at least one point mutation within the motif, and further wherein the mutant receptor generates a signal greater than the wild-type receptor upon interaction with a ligand. The ligand is not set forth in the claim. The claims are anticipated because the Kluxen reference teaches the cloning and expression of a somatostatin receptor (page 4620, Figure 2). The receptor taught by Kluxen meets the structural limitations of the claims in that it comprises a 4 amino acid sequence which that differs from the sequence as disclosed in the instant specification as SEQ ID NO: 1 (see Sequence Comparison A, attached), which is part of the galanin receptor. The somatostatin receptor meets the functional limitation because it will have a larger response to somatostatin than will the galanin receptor. Thus, the somatostatin receptor, when compared to the galanin receptor, meets the structural and functional limitations in the claim. Further, since there is no upper limit to the mutations ("at least one") in the claims are anticipated in which the wild type GPCR is the IL8 receptor. The claim is drawn to a "mutant" mammalian GPCR. There is not a clear definition set forth in the Specification for when a GPCR is to be considered a "mutant". In this rejection, it is being interpreted to cover a naturally occurring variant, and the mutation has come about through evolution. While it is possible that the term "mutant" introduces into the claim the possibility that it is a product by process claim, that is, that the claim would cover only mutant GPCRs wherein the mutation was produced in a laboratory, it is not being interpreted that way, absent a clear definition of

"mutant". Further, even if the term "mutant" were to have any patentable weight, whereby the claim is to be considered as a product by process claim, the Office only examines product by process claims insofar as they read on the product, and does not give patentable weight to the process used for making the product. Thus, the claims are anticipated.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-6, 8, 10-11, 43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kluxen et al. (1992) in view of U.S. Patent No. 5,618,676 (Hitzeman et al.).

The claims are drawn to a mammalian GPCR that comprises a four amino acid motif closer to the C-terminal end, wherein there is at least one point mutation within the motif, and further wherein the mutant receptor generates a signal greater than the wild-type receptor upon interaction with a ligand. The ligand is not set forth in the claim. The claims are not patentable because the Kluxen reference teaches the cloning and expression of a somatostatin receptor (page 4620, Figure 2). The receptor taught by Kluxen meets the structural limitations of the claims in that it comprises a 4 amino acid sequence which that differs from the sequence as disclosed in the instant specification as SEQ ID NO: 1 (see Sequence Comparison A, attached), which is part of the galanin receptor. The somatostatin receptor meets the functional limitation because it will have a larger response to somatostatin than will the galanin receptor. Thus, the somatostatin receptor, when compared to the galanin receptor, meets the structural and functional

limitations in the claim. The Kluxen reference does not teach expression of the protein in yeast. However, the '676 patent discloses that the availability of means for the production in yeast of proteins of choice could provide significant advantages relative to the use of bacteria for the production of polypeptides encoded by recombinant DNA (column 3, line 56). Thus it would have been obvious to one of skill in the art at the time the invention was made to express the mutant GPCR as set forth in the Kluxen reference in a yeast cell as disclosed in the '676 patent. The motivation and expectation of success is provided in the '676 patent which discloses that yeast can be grown to higher densities than bacteria, and is readily adaptable to continuous fermentation processing. Many critical functions of the organism, e.g., oxidative phosphorylation, are located within organelles, and hence not exposed to the possible deleterious effects of the organism's overproduction of foreign proteins. As a eukaryotic organism, yeast may prove capable of glycosylating expression products where important to enhanced bioactivity (column 3, lines 57-67).

Conclusion

Claims 1-11, 43, 61-63, 68 are rejected.

Claims 7, 9 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claims 14, 44-59, 67 are allowable.

References

The Office will no longer be supplying paper copies of U.S. Patents cited in Office Actions. Applicant is advised that the cite

d U.S. patents and patent application publications are available for download via the Office's PAIR. As an alternate source, all U.S. patents and patent application publications are available on the USPTO web site (www.uspto.gov), from the Office of Public Records and from commercial sources. Applicant may direct inquiries about the use of the Office's PAIR system to the Electronic Business Center (EBC) at http://www.uspto.gov/ebc/index.html or 1-866-217-9197.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Murphy whose telephone number is (571) 272-0877. The examiner can normally be reached Monday through Friday from 7:30 am to 5:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (571) 272-0829.

The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR

system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Joseph F. Murphy, Ph. D.
Primary Examiner
Art Unit 1646
September 14, 2005

JOSEPH MURPHY
PATENT EXAMINER

Sequence Comparison A
SEQ ID NO: 1

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RESULT   9
A45291
somatostatin receptor, somatotropin release-inhibiting factor receptor, SRIF receptor -
rat
C;Species: Rattus norvegicus (Norway rat)
C;Date: 25-Mar-1993 #sequence_revision 18-Nov-1994 #text_change 21-Jul-2000
C;Accession: A45291
R;Kluxen, F.W.; Bruns, C.; Lubbert, H.
Proc. Natl. Acad. Sci. U.S.A. 89, 4618-4622, 1992
A;Title: Expression cloning of a rat brain somatostatin receptor cDNA.
A;Reference number: A45291; MUID:92262491
A;Accession: A45291
A;Status: preliminary
A;Molecule type: mRNA
A;Residues: 1-369 <KLU>
A;Cross-references: GB:M93273; NID:g207026; PIDN:AAA42165.1; PID:g207027
A;Note: sequence extracted from NCBI backbone (NCBIN:102315, NCBIP:102316)
C;Superfamily: vertebrate rhodopsin
C;Keywords: G protein-coupled receptor; transmembrane protein


  Query Match             68.4%;  Score 93;  DB 2;  Length 369;
  Best Local Similarity   59.3%;  Pred. No. 3.3e-06;
  Matches   16;  Conservative    6;  Mismatches    5;  Indels    0;  Gaps    0;

Qy       1 LAYSNSSVNPIIYAFLSENFRKRYKQV 27
           | |:||  |||:|||||:||:| :: |
Db     300 LTYANSCANPILYAFLSDNFKKSFQNV 326
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